CHAPTER 39

Depression, anxiety, and delirium

Alan Valentine, MD

Psychiatric disorders are common in the setting of malignant disease, occurring in almost 50% of patients. Many cancer patients cope well with their disease. For those who do not, untreated psychological and neuropsychiatric disorders can seriously compromise quality of life and treatment compliance. Although there is a wide variety of presentations, three behavioral syndromes that are often encountered in clinical practice will be discussed here: depression, anxiety, and delirium.

Depression

"Depression" exists on a continuum ranging from an emotion common in daily life (sadness) to a syndrome of severe physical and psychological symptoms consistent with a defined psychiatric disorder (major depressive disorder).

In cancer patients, identical symptoms may be caused or influenced by physical (eg, tumor site, pain), psychological (eg, stress, premorbid function, maturity), and social (eg, finances, interpersonal relationships) factors. Depression occurs more frequently in the setting of severe illness; several studies of cancer inpatients report a prevalence of 25%–42%.

SIGNS AND SYMPTOMS/DIAGNOSIS

Patients with depressive syndromes experience specific symptoms that vary in intensity and severity.

Psychological symptoms include dysphoria (sadness), anhedonia (pervasive loss of pleasure in activities), feelings of guilt or low self-esteem, and thoughts of death or suicide.

Somatic symptoms include sleep disturbance, change in appetite, loss of libido, fatigue, diminished concentration, and psychomotor agitation or withdrawal.

Focus of diagnostic evaluation Although the diagnosis of major depressive disorder requires that multiple symptoms (including dysphoria or anhedonia) must be present for at least 2 weeks, patients who do not meet these criteria may be in significant distress. The diagnosis of depression in medically ill patients is complicated by the fact that somatic symptoms of depression may

also be caused by factors related to disease and treatment. For this reason, when evaluating the depressed cancer patient, special attention should be paid to psychological symptoms, which are less likely to be directly related to treatment.

ETIOLOGY

Psychological causes

Isolated symptoms Isolated depressive symptoms, if temporally related to an identifiable stressor, may be classified as adjustment disorders. In the setting of malignancy, obvious stressors include the initial diagnosis, treatment failure, or disease progression. Patients may also face potential psychosocial stressors, including changes in independence, body image, finances, and family function, as well as issues related to death and dying.

Persistent symptoms Persistent mood symptoms may indicate the presence of an evolving major depressive disorder. Major depressive disorder is common in the general population (point prevalence, ~6%) and is a recurrent disease. Patients with a history of mood disorder are at risk for relapse in the face of a cancer diagnosis.

Disease- and treatment-related causes

Presenting symptom of malignancy Depression may be a presenting symptom of some primary malignancies, including primary pancreatic and gastric carcinomas. Primary and metastatic brain tumors may cause frontal lobe syndromes or personality changes that mimic depression and other psychiatric disorders.

Drugs Many drugs used in general medical practice are associated with psychiatric syndromes. The most common of these drugs are β-blockers, antihypertensives, barbiturates, opioids, and benzodiazepines.

In contrast, few drugs used as primary and supportive therapies for cancer are commonly associated with depression. The exceptions to this rule are corticosteroids, cytokines (especially interferon-alfa [IFN-α; Intron A, Roferon-A] and interleukin-2 [aldesleukin, Proleukin]), and whole-brain radiation therapy. Depressive syndromes may also be seen with certain chemotherapeutic agents, including asparaginase (Elspar) and procarbazine (Matulane). Patients treated with tamoxifen may complain of depression or "chemobrain." The latter term usually refers to cognitive slowing. Day and colleagues have shown a lack of association between tamoxifen treatment and depression, even in women at higher risk for mood disorders.

MANAGEMENT

Management of depressive syndromes involves accurate diagnosis, use of antidepressant medication, and psychotherapy. Patients should be assessed for somatic and psychological symptoms of depression. The clinician should always ask about suicidal thoughts or intent. Metabolic and thyroid function should be evaluated and medications reviewed.

The decision to treat depression is a matter of clinical judgment. If mood disorder symptoms adversely affect quality of life, work or family relationships, or ability to participate in cancer therapy, intervention is indicated. Because the diagnosis of depression can be difficult to make in patients with cancer, it is best to have a low threshold for the initiation of treatment to minimize the risk of missing a reversible disorder.

TABLE 1: Selected antidepressants used in cancer patients

Drug	Starting dose	Maintenance dose	Comments
Selective serotonin reuptake inhibitors			
Sertraline	25-50 mg qAM	50-150 mg/d	Usually well tolerated; possible nausea
Fluoxetine	10-20 mg qAM	20-60 mg/d	Long half-life; possible nausea, sexual dysfunction
Paroxetine	20 mg/d qAM	20-60 mg/d	Possible nausea, sedation
Escitalopram	10 mg/d	10-20 mg/d	Usually well tolerated; possible nausea, sexual dysfunction, fatigue
Tricyclic antidepressants			
Nortriptyline	25-50 mg qhs	50-200 mg/d	Moderate sedation; useful for neuropathic pain
Amitriptyline	25-50 mg qhs	50-200 mg/d	Maximal sedation; anticholinergic effects; useful for neuropathic pain
Desipramine	25-50 mg qAM or hs	50-200 mg/d	Modest sedation; anticholinergic effects; useful for neuropathic pain
Other agents			
Venlafaxine	18.75-37.5 mg	75-225 mg/d	Possible nausea; may be useful for neuropathic pain, hot flashes
Bupropion	50-75 mg	150-450 mg/d	Activating; no reports of sexual dysfunction; risk of seizures in predisposed patients
Methylphenidate	5 mg (2.5 mg qAM, noon)	10-60 mg/d	Activating; rapid effect possible; monitor blood pressure
Mirtazapine	15 mg qhs	15-45 mg qhs	Sedating, variable appetite-stimulant, antiemetic effects

Antidepressants

Selected antidepressants used in cancer patients are listed in Table 1. No antidepressant has been shown to be more effective than any other in the cancer setting. Often, the choice of an antidepressant is based on side-effect profile.

In the general population, antidepressants often take at least 2 weeks or longer to produce initial relief of symptoms. There is some anecdotal evidence that a more rapid effect is seen in cancer patients. As a general rule, antidepressant therapy should continue for 4-6 months after symptoms stabilize.

Selective serotonin reuptake inhibitors (SSRIs), such as fluoxetine (Prozac, Sarafem), sertraline (Zoloft), paroxetine (Paxil), and escitalopram (Lexapro), are often used in patients with cancer because of their benign side-effect profile. In particular, their lack of anticholinergic and α-adrenergic–blocking properties makes them attractive options for patients with a serious medical illness.

Unlike the tricyclic agents (discussed below), the SSRIs are not lethal in overdose, making them a safe choice in the treatment of patients experiencing suicidal ideations.

Side effects Mild nausea and anxiety are common side effects of all SSRIs, which vary in severity from patient to patient. Sexual dysfunction may occur with fluoxetine and paroxetine. Sedation may occur with paroxetine.

Dosage In ambulatory patients with normal metabolic function, SSRIs can be started at the same doses used in general psychiatry (ie, 20 mg/d qAM for fluoxetine, 50 mg/d qAM for sertraline, 20 mg/d qAM for paroxetine). These doses can be increased if there is no response within 2-3 weeks.

Hospitalized or elderly patients, those with compromised renal or hepatic function, and those receiving highly emetogenic treatments should be started at one-half or even one-quarter of these starting doses, which can then be increased if tolerated.

Tricyclic antidepressants (TCAs) These older antidepressants (eg, amitriptyline, nortriptyline, and desipramine) remain effective options for the treatment of depression in cancer patients. The sedative properties of TCAs can be useful in the treatment of insomnia associated with depression. In addition, TCAs are useful adjuncts in the treatment of neuropathic pain.

TCAs have the advantage of established therapeutic blood levels, although the applicability of these levels to cancer patients is uncertain.

Side effects The common side effects of TCAs include sedation, dry mouth, orthostatic hypotension, constipation, and blurred vision. These side effects are related to anticholinergic, α-adrenergic–blocking, and antihistaminic properties of TCAs and are often the reason these drugs are not used as the first line of treatment in depressed medically ill patients. TCAs must be used cautiously in patients with active suicidal ideations and in those with cardiac conduction abnormalities.

Dosage Initial dosing of TCAs should be conservative (25-50 mg PO qhs for nortriptyline, 25-50 mg qhs for amitriptyline, 25-50 mg qAM or hs for desipramine), with escalation of doses if tolerated every 4-7 days. Therapeutic response is sometimes seen at doses lower than those used in the general population, that is lower than 75-150 mg/d for nortriptyline, 150-300 mg/d for amitriptyline, and 200-300 mg/d for desipramine.

Atypical and newer antidepressants Bupropion (Wellbutrin) is activating, which may be of potential benefit in patients with psychomotor slowing. Another advantage is that it is not associated with sexual dysfunction. However, bupropion has been associated with seizures and therefore should be used with caution (if at all) in patients who suffer from seizures or who have a history of seizures.

Venlafaxine (Effexor), nefazodone (Serzone), and mirtazapine (Remeron) are newer agents with selective effects on serotonin and norepinephrine metabolism. They should be started at low doses to establish whether they can be tolerated. Venlafaxine may be effective against treatment-induced hot flashes. Mirtazapine has sedative, appetite-stimulant, and antiemetic effects, which can be very useful in selected cases.

Psychostimulants

Psychostimulants that have direct or indirect dopamine-agonistic properties, such as dextroamphetamine, methylphenidate, and pemoline, have an established role in the treatment of depression in the medically ill. Psychostimulants are activating agents useful in patients with psychomotor retardation, deconditioning, or apathy states associated with depression, as well as in those with CNS disease or treatment side effects.

The antidepressant effects of psychostimulants may be seen more quickly than those of first-line antidepressants. Improvements in mood, physical activity, well-being, and appetite are sometimes observed within 24-48 hours of the initiation of psychostimulant treatment.

Side effects Like other activating agents, psychostimulants may cause insomnia, anxiety, palpitations, and GI upset. Hypertension or hypotension may also occur.

Dosage Initial dosing should be conservative (eg, 5 mg/d in two divided doses every morning and noon for methylphenidate, 5 mg/d qAM for dextroamphetamine). If tolerated, stimulant doses can be increased until a therapeutic effect is achieved or side effects develop.

Psychotherapy

Although antidepressants alone are effective in the treatment of depression, patients often require and benefit from psychotherapy.

In some cases, such therapy can be limited to support while response to medication is monitored. Other patients may require cognitive-behavioral interventions to help them deal with misperceptions about their disease status or to resolve preexisting issues.

For some patients, group therapy can be helpful, although others find it difficult to interact with patients who are equally or more severely ill.

Anxiety

Like depression, the term "anxiety" refers to both a subjective emotion and a constellation of signs and symptoms that can be of physical or psychological origin.

Especially in seriously ill patients, subjective anxiety may be the first sign of a serious or catastrophic medical event. It is also common at disease milestones, especially at initial diagnosis, time of recurrence, and progression to the terminal phase. In patients whose disease is stable or in remission, anxiety frequently occurs before or at the time of routine reevaluation.

SIGNS AND SYMPTOMS/DIAGNOSIS

Psychological symptoms Patients who experience anxiety typically complain of feeling worried, irritable, and frightened. They may appear depressed; there is considerable comorbidity between the two syndromes. Patients are often hyperalert and hypervigilant. The affective state is labile; individuals may cry suddenly or experience paroxysmal temper outbursts. Thought processes are ruminative; individuals cannot distract themselves from worry.

If anxiety proceeds to panic, patients may experience feelings of impending doom or annihilation. Occasionally, distress is so intense that patients experience suicidal thoughts. The hyperaroused state makes sleep difficult and impairs appetite. Physical and psychological fatigue and exhaustion may follow.

Physical symptoms Numerous physical symptoms may be experienced, especially as anxiety becomes more severe.

Cardiovascular signs and symptoms include palpitations and tachycardia, as well as subjective chest tightness or pain.

Respiratory symptoms include dyspnea; patients may hyperventilate and feel light-headed or dizzy.

GI symptoms are common and include difficulty in swallowing, abdominal cramping, nausea, diarrhea, and constipation.

Patients may become diaphoretic. Preexisting pain may be aggravated.

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Psychological causes

For many patients, the diagnosis of cancer is extremely stressful. Anxiety is often a function of fear. Patients anticipate the possibility of pain, suffering, or death. Concerns about loss of control and independence, finances, and family obligations also contribute.

Painful or unpleasant diagnostic or therapeutic procedures and medications may lead to anxiety, which can become conditioned. For example, conditioned anxiety states, such as anticipatory nausea, develop in some individuals after such treatments as chemotherapy and confinement for bone marrow transplantation.

Patients who achieve remission often worry about possible recurrence. Associated anxiety may become more pronounced shortly before clinic visits or tests.

Anxiety may also become more pronounced when active treatment ends. In some cases, the process of diagnosis and treatment is so psychologically difficult that a post-traumatic stress disorder develops.

Generalized anxiety disorder and panic disorder are relatively common in the general population. Affected individuals are at risk for exacerbation of the anxiety disorder in the face of a cancer diagnosis. Individuals who have specific phobias (eg, to blood, needles, or hospitals) will likely suffer intense anxiety at diagnosis or during treatment and may require referral to a mental health specialist.

Especially in the elderly, anxiety may mask an underlying mood disorder, usually depression.

Disease- and treatment-related causes

Toxic metabolic states Hypoxia should be the initial metabolic consideration in anxious patients. Possible causes include anemia and pulmonary edema.

Anxiety may be the initial manifestation of pulmonary embolus.

Electrolyte disturbances may cause anxiety, especially if they are severe or occur in the setting of CNS impairment.

Endocrine disturbances (eg, hyperthyroidism, hypercalcemia, and hyperadrenalism) also can cause anxiety. These endocrine disturbances may be preexisting conditions, a function of disease, and/or a side effect of treatment.

Anxiety may be an early sign of sepsis.

Drugs Several medications commonly used in oncology may cause anxiety of variable severity. For example, corticosteroids can produce anxiety that varies from mild nervousness to frank agitation resembling mania.

Antiemetics, including promethazine, prochlorperazine, and metoclopramide, are associated with akathisia, a sense of internal restlessness and anxiety that compels patients to move in order to achieve relief. The anxiety can be quite severe; patients suffering from severe akathisia have attempted suicide. Antipsychotic medications (eg, haloperidol and chlorpromazine) also can cause akathisia.

Anticholinergic medications (eg, benztropine mesylate [Cogentin]), opioids, and benzodiazepine anxiolytics can cause paradoxical reactions that include anxiety; this is especially true in geriatric patients and in those with CNS impairment.

Drug toxicity (eg, from immunosuppressants, bronchodilators, psychostimulants) and drug withdrawal states (eg, from opioids, benzodiazepines, and alcohol) often produce anxiety, which may evolve into delirium.

Disease factors The most important of these factors is inadequate pain relief, which may cause or exacerbate anxiety and depression. Hormone-secreting tumors (eg, pheochromocytomas, small-cell lung tumors, and some thyroid carcinomas) also may cause paroxysmal symptoms of anxiety or panic.

MANAGEMENT

The initial approach to anxious patients depends on the severity of anxiety and their medical status. In all cases, the multiple possible medical causes of anxiety should be considered and addressed or corrected. In some cases, it is not possible to remove offending medications (ie, corticosteroids), and symptomatic relief must be provided while these agents continue to be used.

Psychotherapy

Supportive therapy for anxious patients is universally appropriate. Anxious patients benefit from reassurance that they are not alone, that help is available, and that action will be taken to help them deal with the cause of their distress.

Patients suffering from phobic or conditioned anxiety states, as well as those with anxious depression, may benefit from specialized treatment, including cognitive therapy, guided imagery, self-relaxation training, and biofeedback. These techniques, which may require referral to a specialist, provide patients with a sense of control and teach skills that can be applied to minimize future threats.

Anxiolytics

Benzodiazepines are the mainstays of pharmacologic treatment of anxiety. These medications are generally safe and effective. Selected benzodiazepines that are commonly used to treat anxiety in cancer patients are listed in Table 2. Issues related to dependence or oversedation are usually not of major concern.

Benzodiazepines have variable hypnotic, antiemetic, and muscle-relaxant effects useful in other aspects of supportive care of cancer patients. Caution is required when these agents are used in the settings of serious illness (because of the risk of additive sedation with other medications), advanced age, or CNS impairment (because of the risk of disinhibition or delirium).

Short-acting benzodiazepines, such as lorazepam and alprazolam, have a rapid onset but relatively short duration of action, making them useful for treating intermittent paroxysmal anxiety or panic attacks. For the same reason, they are also useful in patients with severe medical illness.

Typical doses are 0.5-1.0 mg PO/IM/IVP/IVPB (lorazepam) every 4 to 12 hours or 0.25-0.5 mg PO (alprazolam) every 6 to 8 hours as needed. For patients with persis-

TABLE 2: Selected benzodiazepines used to treat anxiety in cancer patients

Drug	Dose range (prn or scheduled)	Comments
Lorazepam	0.5-2.0 mg PO/IM/IVP/IVPB q4-12h	Versatile; favorable metabolic profile useful in the severely ill; can be administered via continuous infusion in rare cases
Alprazolam	0.25-1.0 mg PO q6-24h	Potent, rapid onset and cessation of effects; tolerance may develop quickly; antidepressant effects
Diazepam	2-10 mg PO/IM/IV q6-24h	Useful for general/persistent anxiety but problematic in elderly or seriously ill patients
Clonazepam	0.5-2.0 mg PO q6-24h	Useful for general/persistent anxiety, episodic anxiety, and aggressive behavior in some CNS-impaired patients

IVP = IV push; IVPB = IV piggyback

tent anxiety, these medications can be given on a regular schedule.

In cases of extremely severe anxiety, lorazepam may be administered via continuous infusion. Its lack of active metabolites makes it a good choice in patients with hepatic or renal compromise.

Tolerance develops more rapidly to short-acting benzodiazepines than to their longer-acting counterparts. Therefore, if short-acting agents are used for any length of time, they should be discontinued gradually.

Longer-acting benzodiazepines, such as diazepam and clonazepam, are useful for persistent anxiety. Their longer duration of action is such that they do not "wear off" quickly, leaving patients unprotected. Tolerance does not develop as quickly to these agents, and patients with generalized anxiety disorders may be maintained on them for years.

Clonazepam is typically given at a dose of 0.5-1.0 mg every 6 to 8 hours on a scheduled basis, whereas the diazepam dose typically starts at 2-10 mg every 6 to 24 hours. Higher doses are often required.

These drugs have multiple active metabolites that can adversely affect the elderly and patients with renal or hepatic impairment. In such patients, it is best to "start low and go slow."

Antidepressants are becoming mainstays of pharmacologic treatment of chronic anxiety disorders, including generalized anxiety disorder, panic disorder, and social phobia. Use of these medications avoids the issues of side effects and tolerance associated with benzodiazepines. The antidepressants are also attractive in this setting because anxiety and depression are frequently comorbid conditions.

Currently, paroxetine and escitalopram have FDA indications for the management of generalized anxiety disorder, as does venlafaxine. Most of the SSRIs have been used successfully in the treatment of panic disorder. Typically, it takes 2 to 4 weeks before the antianxiety effects of these medications are noted. It may be useful or necessary to use a short-acting benzodiazepine as adjunctive therapy until the antidepressant takes effect. Typical dose ranges for these agents follow: paroxetine, 20-40 mg/d; escitalopram, 10-20 mg/d; sertraline, 50-150 mg/d; and extended-release venlafaxine, 75-225 mg/d (see Table 1).

Other medications At low doses, antipsychotic medications, such as thioridazine, haloperidol, olanzapine (Zyprexa), quetiapine (Seroquel), and risperidone (Risperdal), may be used as anxiolytics. These agents are most appropriate for patients with a history of, or at high risk for, adverse reactions to benzodiazepines.

Opioid analgesics are effective anxiolytics in some terminally ill patients, especially those patients in whom compromised respiratory function is a cause of anxiety.

Delirium

Delirium (also known as encephalopathy and acute confusional state) is the most common mental disorder of purely organic origin in the cancer setting. This syndrome is characterized by diffuse brain dysfunction, caused by one or more pathologic factors related to the disease or its treatment.

The prevalence of delirium is a function, in part, of the severity of medical illness. In some surveys, 15%-30% of cancer inpatients and up to 85% of those who are terminally ill experience delirium. The overall prevalence of delirium in the inpatient setting is expected to increase with the aging of the general population.

SIGNS AND SYMPTOMS/DIAGNOSIS

The onset of delirium is acute, within hours to days, and is characterized by alterations in arousal, perception, and cognition. There may be a prodromal phase of irritability or anxiety.

Alterations in arousal Delirious patients demonstrate a sensorium (or level of alertness) that varies from hyperalert and vigilant to obtunded or stuporous. Psychomotor activity varies in a similar way; a hyperactive or hypoactive delirium may be encountered.

Alterations in perception/cognition Delirious patients may have perceptual difficulties, with illusions and hallucinations, which they cannot distinguish from reality. Patients may also experience delusions, often of the paranoid type. Typically, patients have lucid intervals (minutes to hours) during which their mental status appears to be appropriate and intact. Cognition is impaired because patients cannot attend to and register new information.

Other signs/symptoms Typically, delirious patients have a disordered sleep/wake cycle, which may be a function of the delirium or a preceding cause.

Autonomic dysfunction may be encountered in patients with hyperaroused states.

Left untreated, delirium may resolve spontaneously or evolve into another neuropsychiatric disorder. Failure of delirium to resolve with aggressive management may signal a preterminal event.

ETIOLOGY

Disease- and treatment-related causes

As with anxiety states, delirium can have many possible causes in cancer patients. Often, the etiology is multifactorial, and in up to 50% of cases, a definite etiology cannot be identified.

Direct and indirect disease effects Primary and metastatic brain tumors will occasionally present as delirium, as will leptomeningeal carcinomatosis and paraneoplastic syndromes. Most, but not all, patients with these diseases also have frank neurologic signs.

Toxic metabolic abnormalities Hypoxia, which often causes anxiety, may also produce delirium, especially as a function of a rapidly evolving insult.

Severe electrolyte disturbances, especially sodium and potassium, may cause delirium, as may altered serum calcium and magnesium levels.

Other common toxic metabolic causes of delirium include liver and renal failure, systemic or CNS infection, and severe nutritional deficiencies.

Cancer therapies Corticosteroids, which are ubiquitous in cancer treatment, produce a wide variety of psychiatric side effects, including an agitated psychotic state that resembles delirium.

Irradiation of the brain occasionally causes delirium, which typically begins during or immediately after the completion of treatment. This side effect is thought to be due to edema and raised intracranial pressure. It is usually controlled or prevented by corticosteroid therapy.

Chemotherapeutic and biotherapeutic agents Many chemotherapeutic and biotherapeutic agents have been associated with delirium or encephalopathic states, although some are more often responsible than others. They include ifosfamide (Ifex), methotrexate, and cytarabine (cerebellar syndrome). Interleukin-2, alone or in combination with IFN-α, may cause agitated delirium. Toxic levels of immunosuppressants (eg, tacrolimus [Prograf]) and antiviral agents also have been associated with encephalopathies.

Other drugs Benzodiazepines, opioid analgesics, and anticholinergic medications (eg, benztropine mesylate) can induce delirium in certain situations. Usually, this problem occurs when high doses of these agents are used in seriously ill patients. However, the elderly and patients with CNS compromise are vulnerable to this adverse effect when given low doses, especially at night.

Severe alcohol withdrawal is a common cause of hyperactive delirium.

MANAGEMENT

Evaluation

Initial management of delirium involves a search for a reversible cause. In all cases, physical and neurologic examinations are indicated. An exhaustive work-up for all possible causes is usually not necessary. The patient's clinical situation and known history should provide guidance. Attention should be paid to the patient's metabolic and respiratory status. Evaluation of hepatic and renal function should be completed.

The role of prescribed and illicit medications, chemotherapeutic agents, and biotherapeutic agents should be considered.

Diagnostic tests Diagnostic imaging of the brain (eg, CT, MRI) may be indicated. In some cases, electroencephalography may help establish the presence of an encephalopathic state. Assessment of CSF is appropriate for patients with suspected CNS infection or leptomeningeal carcinomatosis.

TABLE 3: Selected medications used to treat delirium in cancer patients

Drug	Dose range	Comments
Antipsychotics		
Haloperidol	0.5-2.0 mg PO/IM/IVPB/SC q4-12h	IV route twice as potent as PO route and has fewer side effects; 2.0–5.0-mg bolus/continuous infusion for severe agitation
Chlorpromazine	25-100 mg PO/IM/IVP/IVPB q4-12h	Very sedating; may be administered as continuous infusion; monitor blood pressure
Risperidone	0.5-3.0 mg PO q12-24h	Useful in elderly patients; may pose lower risk of parkinsonian effects; not useful for severe agitation
Olanzapine	2.5-5.0 mg PO q8-12h	Zydis formulation is an orally disintegrating tablet that is easily swallowed
Benzodiazepine		
Lorazepam	0.5-4.0 mg PO/IM/IVP/IVPB q4-12h	Most effective when used with an antipsychotic; when used alone can exacerbate delirium; may be administered as a continuous infusion
Anesthetic		
Propofol	10-50 mg IV qh	Rapid onset, short duration of action; not an antipsychotic; dose can be titrated to desired level of sedation

IVP = IV push; IVPB = IV piggyback

Behavioral management

The patient's safety must be secured. Depending on individual circumstances, this may require close observation, use of physical restraints, or neuroleptic medications. Unless there is a medical contraindication, restraints should not be used without medications to assist in calming the patient.

Ideally, patients should be managed in a setting of moderate environmental stimulation. Both sensory overstimulation and deprivation are disadvantageous. Because delirious patients are often anxious or frightened, the presence of family members can provide reassurance.

Antipsychotics

If more conservative measures are ineffective, pharmacotherapy is required to treat delirium. Antipsychotic medications treat sensory and cognitive misperceptions as well as provide anxiolysis and some degree of sedation. Table 3 lists selected drugs often used to treat delirium in cancer patients.

Haloperidol is a potent antipsychotic that may be administered by PO, IM, IV, or SC routes (with the SC route often used for terminal delirium). The IV formulation is twice as potent as the PO preparation.

Side effects Haloperidol is usually well tolerated, although it does carry a risk of producing akathisia and parkinsonian side effects. These side effects can be treated with benztropine mesylate, benzodiazepines, or other medications. The risk of these adverse reactions can be minimized by IV administration.

Dosage Elderly patients or patients with end-stage disease usually require very modest doses (0.5-1.0 mg PO or IV at night or twice daily) to control delirium. Especially in hyperactive delirium, higher and more frequent dosing is usually required (eg, 2-5 mg PO/IVPB every 6 hours). Total doses of ≥ 100 mg/d may be administered via a continuous infusion in unusual cases.

Chlorpromazine is a potent antipsychotic that is more sedating than haloperidol and may be administered by the same routes. Typically, chlorpromazine is given at a dose of 25-50 mg PO/IVPB every 6 to 12 hours. Rapid calming of an agitated patient may require IM or IV doses of 50-100 mg. Chlorpromazine can be given by IV infusion if necessary.

Chlorpromazine has significant anticholinergic and α-adrenergic–blocking effects, which can be problematic if used in seriously ill patients or elderly patients vulnerable to hypotensive episodes.

Risperidone is given orally. At doses of 0.5-3.0 mg once or twice daily, it is useful in treating low-intensity delirium or delusional symptoms, especially in elderly patients, in whom it may have fewer adverse effects than oral haloperidol. Risperidone is not useful for treating acute agitation.

Olanzapine has been shown to be effective in the management of delirious cancer patients. Though it is not available for parenteral administration, the Zydis formulation of olanzapine is an orally disintegrating tablet that easily dissolves in the mouth and may be useful for some agitated patients and those with swallowing difficulties.

Other agents

Benzodiazepines are used as adjuncts in the control of hyperactive delirium. They are the treatment of choice for alcohol withdrawal delirium. Lorazepam, 0.5-4.0 mg IV or IM, may be given with haloperidol to rapidly control acute agitation. It is sometimes effective to alternate doses of lorazepam and haloperidol every 30 minutes until the patient falls asleep.

Benzodiazepines do not have antipsychotic properties and, if used by themselves, will exacerbate disinhibition and cognitive impairment of a delirious patient, unless a sufficiently large dose is given to cause sleep.

Propofol is a short-acting anesthetic that is effective in achieving rapid sedation. It is often administered as a continuous IV infusion in the ICU setting. Propofol does not have antipsychotic properties.

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